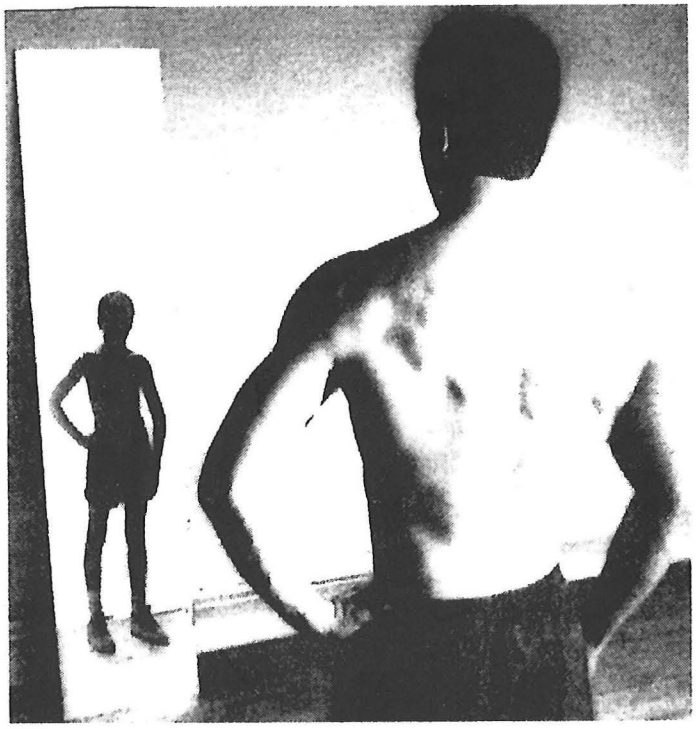
The Science Of Androgen Abuse, From The Athlete's Perspective



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This is to acknowledge that Richard J. Auchus, MD, PhD, has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Auchus will be discussing off-label uses in his presentation.

Dr. Auchus' research interests include the genetics and biochemistry of human steroidogenic enzymes with emphasis on the structural basis of substrate discrimination, product distributions, and reaction mechanisms. His clinical practice focuses on pituitary, adrenal, and gonadal disorders, including endocrine hypertension and adult patients with genetic disorders of steroid biosynthesis.

Today's lecture will address:

1) What are androgens/anabolic steroids
2) Who uses these agents and why; patterns of use
3) Evidence of efficacy; possible mechanisms of action
4) Types and severity of side effects
5) Detection methods; how reliable are they
6) Newer agents of abuse and "nutraceutical" precursors

In light of Jean Wilson's recent presentation about the quandary over the use of performance enhancing drugs in competitive sports at these exercises, I will touch on topics that he covered for the benefit of those who did not attend, but I will focus on:

- "Recreational users," their motivations, their psyche, why some become addicted to androgens
- Nutraceutical precursor steroids, their metabolism, and implications for detection methods, and implications for mechanisms of action

I. Definitions

Androgens: compounds that bind to the androgen receptor and elicit androgenic *biological activity*. The two key androgens produced in human beings are testosterone (T) and dihydrotestosterone (DHT).
Androgenic: masculinizing (i.e. deepening of voice, hair changes in androgen-dependent areas, phallic growth, labioscrotal fusion); virilization refers to the masculinization of the genitals, and it indicates very substantial androgen action.
Anabolic: aiding in the assimilation of food into tissues, such as nitrogen into muscle.

The German pharmaceutical industry spent much effort attempting to develop synthetic steroids that had anabolic activity but lacked androgenic effects, but they were never successful. More detailed understanding of androgen receptor function and structure have led to renewed attempts by companies like Ligand Pharmaceuticals to develop "SARMs," yet no definitely successful reports have yet been disclosed. Because of this lack of success, it has been assumed that the anabolic and androgenic actions are inseparable. Furthermore, patients with complete testicular feminization who lack functional androgen receptors do not experience any androgenic effects when exposed to endogenous or exogenous androgens. Does this mean that the anabolic effects of androgens must be mediated via the androgen receptor? We will explore this later.

II. Users and Use Patterns

Who uses androgens?

It is useful to propose two dichotomies to classify androgen users because their motives, risks, and patterns of use are different. The first dichotomy is that of professionals versus recreational users. Professionals have clearly defined goals and schedules for competition, including drug testing, so they have to stop usage for at least some defined periods. Regretably, the use of androgens in many professional sports (football, powerlifting, etc.) is so pervasive that these athletes are practically destined to use them else fail to compete with the physical advantages of the users. We will focus on recreational users in the first half of the talk. The second dichotomy is male versus female users. Numerous studies document the lower use of androgens in females versus males at both the professional and recreational level, most likely due to the bizarre but predictable physical changes that virilizing drugs impart on women. Amongst elite athletes, androgen use appears to be most extensive (and infamous) in track/field and sprint swimming events (compare Janet Evans and Jingyi Le). Recent observations, however, suggest that use in women also is becoming more pervasive in what are not traditionally "strength" events simply because the drugs enable more intense training (and strength never hurts). In sports where size and weight can be disadvantageous, the doses and periods of use are more controlled to reap the benefits of the residual effects while avoiding consequences of prolonged exposure.

Where do they get androgens?

Jean covered this topic, but I will add two comments. The first is that 50% of users are adolescents, and although some choose to obtain and use androgens through their friends, many parents and coaches will start children on androgens, particularly boys in sports like football where size and strength are paramount. This practice is like snorting cocaine with your kids, but these adults fail to see any risk in this practice. The second comment is that under the regulations set forth in the DSHEA act of 1994, precursors to androgens are now legally distributed for sale as "dietary supplements." We will focus on this topic in the latter half of the talk.

Why do they use androgens?

Individuals who use androgens to enhance athletic performance only compromise a minor proportion of users. Adolescent males believe that a large, muscular physique will garner more social popularity, and this perception is admittedly fairly accurate. Thus, many teenage boys use androgens to bulk up to be more socially attractive to the majority of their peers that have the same perception(1). Up to 30% of adolescent users neither compete in sports nor train/bodybuild but simply take androgens to gain weight and size (referred to as "joy riders"). On the other hand, a large group of users consists of men who exercise compulsively, striving to be ever more large and muscular without limit. Within this group, a subset have a curious underlying psyche that predisposes them for escalated use and addiction. Harrison Pope and colleagues at the McLean Hospital in Belmont, MA have studied this group extensively and have coined the terms "reverse anorexia nervosa" and more recently "muscle dysmorphia" (MD) to characterize men who are muscular by conventional standards but who perceive themselves to be small and who are frankly embarrassed by their perceived lack of size(2).

Recently this group published a study in which they canvassed gymnasiums asked for volunteers to complete a survey. In the first series, they asked for men who could bench press their own weight at least 10 times yet still are concerned that they look small (the MD group). For a control group, they later solicited men who could bench press their own weight at least 10 times and had been weightlifting for at least 2 years. The MD group reported that they spent, on the average, over 6 hours per day preoccupied with being small. They also showed a dramatic reluctance to expose their upper body in public and evidence of both compulsive exercising (to get bigger) and checking mirrors to evaluate the results of their training(3).

Muscle Dysmorphia

Characteristics

	M.D.	Con.
Number of Times You Weigh Yourself/Week	5.0	2.0
Number of Times You Check Mirrors/Day	9.2	3.4
Minutes/Day Preoccupied Being Small	325	41
Have You Worn Heavy Sweatshirts In Summer Or Refused To Remove Shirt?		
Yes	21	0
No	3	30
Have You Given Up Enjoyable Activities To Go To The Gym To Get Bigger?		
Yes	24	11
No	0	19

Olivardia et al Am J Psychiatry 157:1291-1296 (2000)

The combination of androgen usage and the MD personality is a particularly problematic combination. As we will see, supraphysiological doses of androgens do work to increase weight and strength, which is what the MD group desires. In addition, high doses of androgens impart a feeling of euphoria and invincibility, which can progress to mania and violent behavior(4). However, withdrawal of androgens at the end of a cycle results in loss of this vigor and, worse yet, relatively rapid loss of muscle bulk. This distressing consequence causes MD users to return to androgen use, to escalate the dose with each cycle, and to shorten the time between cycles. As is the case with any other substance that is self-administered to achieve a psychological result (alcohol, nicotine, cocaine), this feedback process leads to addiction. Psychological dependency on androgens is common, particularly in the MD population, and physical dependence has been reported in at least one case report of a vasomotor instability syndrome responsive to clonidine(5). This is why androgens are now C-III controlled substances.

These dependent users experience an androgen withdrawal syndrome, and the severity depends on the dose and duration of use, their underlying psyche, and other factors. Withdrawal consists of two phases(6): the early phase is marked by agitation and possibly vasomotor instability as the addict experiences the neurological sequellae of acute androgen withdrawal as well as the anticipatory distress of the impending weeks without androgens. The aggression and manic tendencies caused by high doses of androgens can create a hostile situation that may require hospitalization of the patient for the threat that he/she poses to self and to living partners, children, and close contacts. The second phase can last for months, depending on the prior duration of use. Lassitude, loss of vigor, and frank major depression can occur, particularly in the MD users whose feelings of self-worth are particularly dependent on the size gains brought by the androgen usage. Furthermore, the patient often reverts not to a state of normal circulating androgen concentrations but rather to hypogonadism due to H-P-G axis suppression, and thus they are particularly disadvantaged in trying to maintain any exercise and fitness regimen.

Treatment of individuals who have self-administered huge doses of androgens for long periods of time is controversial and anecdotal at best, but I will propose a few principles here. First, the process should be considered similar to any other type of drug withdrawal in that ancillary psychological therapy and establishing patient rapport are critical for success. I make it a point, for the rare motivated individual who seeks medical attention for permanent withdrawal, to applaud their desire to be fit. I encourage them to continue to exercise, but we try to set realistic goals. I also emphasize the importance of good nutrition (although they often know more about this topic than I do) and good sleep habits. Many of these people live on little sleep during the manic phase of androgen use, and with the loss of this drive, especially if they continue working out, they will need lots of sleep. In addition, gonadotropins pulse more during deep sleep, which will aid in H-P-G axis recovery.

Early in the process, agitation and violent behavior may require hospitalization and benzodiazepines or haloperidol administration(6). A prophylactic course of SSRIs for the depression that later ensues is very reasonable in at-risk subgroups(7). Although there is no need to taper the androgen dose, this process is often required to ensure patient follow-up, but you should immediately set a time frame to arrive at a physiological replacement dose (1-2 months). Transdermal testosterone preparations may be preferable

because they cannot really be abused, as even really big guys have only so much surface area. At this point, going "cold turkey" is an option, but switching to a 50% replacement dose of injectable testosterone (100 mg every 2 weeks) or skipping transdermal doses once, then twice, then three times a week is usually more acceptable. I monitor morning trough testosterone and gonadotropin concentrations, and if these become normal, it is time to stop. Addition of hCG (which acts like LH at the LH/CG receptor on the Leydig cells) does improve testicular size partially and may help with recovering endogenous testosterone production, but it will not help axis recovery and it is expensive, so I use it sparingly unless fertility is an issue. Fertility can be restored with prolonged withdrawal, but it can be permanent. Gonadotropins (hCG + FSH) or GnRH pumps are effective for increasing sperm counts, but they are very expensive.

How are androgens self-administered?

Again, Jean covered the concept of stacking and cycles(8), but I wish to point out that the concept in the minds of the users is not to minimize the side effects of each agent by spreading the dose out amongst several androgens. Instead, they are convinced that some androgen preparations have specific beneficial effects. For example, most serious androgen-dependent bodybuilders add nandrolone decanoate (injectable 19-nortestosterone ester, Deca-Durabolin or "Deca") to their regimen for the unassailable belief that this agent specifically prevents tendon rupture, one of the only consequences of androgen abuse that they actually worry about. Whether this is true or not is not clear, but this persistent reliance on nandrolone esters makes them vulnerable to standard drug testing methods, as we will see. Furthermore, some side effects are handled not by dose reduction but by the use of ancillary agents such as tamoxifen (antiestrogen) and testolactone (aromatase inhibitor) to counteract gynecomastia; tretinoin (Retin-A) for the inevitable acne, and hCG for testicular atrophy. Many of these drugs are not cheap, and this can be an expensive habit. Nevertheless, the detailed usage of several agents points out that this subculture has done extensive investigation in their own observational manner. These people are informed and sophisticated, and they profoundly distrust the medical community because we have discounted the efficacy and value of androgens as anabolic agents for so long.

III. Efficacy and Mechanism of Actions

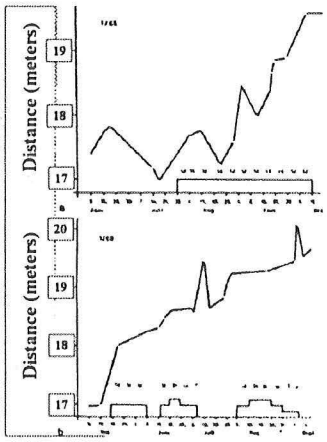
Well, do androgens really work to improve strength/weight/performance?

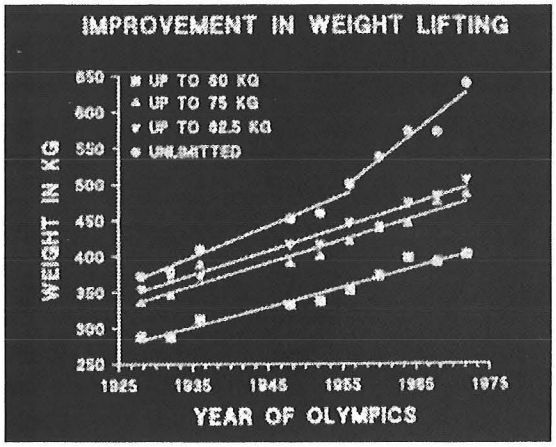
I think that most of us in medicine, as well as the general public, really did not want to believe that supraphysiologic doses of androgens are so dramatically effective in promoting muscle hypertrophy and performance because it reduces success in many sports—something so ingrained and central to or culture and heritage, to a technology rather than a human pursuit. Particularly for Americans, where our economy and national spirit is built on concepts of rugged individualism and fair competition, the thought that a drug can make the difference between winning and losing was particularly repulsive. The feminist movement has made fantastic strides in promoting equality for the sexes, yet the concept that "male hormones" alone can make people "better" was

likewise threatening and distasteful. Nonetheless, abundant anecdotal reports and pervasive use alone made a compelling case for androgen efficacy. Amongst older studies, methandrostenolone (Dianabol) seemed to consistently show benefit for continuously training subjects when maximum, single repetition lifts (1-RM) were assessed. Nevertheless, doses used in these studies were puny compared to the massive amounts used by professionals and recreational users alike.

The secret East German records contain numerous impressive "n of one" experiments that show, particularly in women, the effect of their drug of choice, oral-turinabol (a chlorinated 17-methyl testosterone derivative), in weight events of track and field (shot put, etc.) and in sprints (track, swimming)(9). In addition, a plot of winning lift versus year for weightlifting shows a distinct discontinuity in the curve about the time that androgen use became widespread, but only in the unlimited weight class.

Oral-Turinabol Effect On Shot Put Distance, GDR Female Athlete





Finally, Bhasin and colleagues randomized young, healthy, untrained men to no treatment, exercise alone, testosterone alone, or testosterone + exercise(10). The testosterone dose was 600 mg/week, about 6-8 times physiologic. Note that these subjects averaged about 80 kg and consumed 3,000 calories per day with 120 g protein. The greatest gains in weight, strength, and size were in the testosterone + exercise group, and the two interventions appeared to give somewhat additive effects. Closer inspection of the data, however, shows that the greatest gains in strength *per unit weight gain* occurred in the exercise alone group. Bhasin and colleagues also recognize this phenomenon as less strength per increment in muscle area, the concept of muscle "specific tension," but they have no explanation for this result so far. Perhaps this is the reason we only see the discontinuity in the curve for the unlimited class of weightlifters. Bhasin's group has also gone on to obtain some dose-response data but going to lower and not higher doses; these data have not been published.

Supraphysiologic Testosterone

	No Exercise		+ Exercise	
Change	Plac.	Test.	Plac.	Test.
Weight (Kg)	1.3	3.5	0.9	6.0
Quads (mm^2)	0	600	530	1,200
Bench (Kg)	0	9	10	22
Squat (Kg)	3	13	25	38

Bhasin et al NEJM 335:1-7 (1996)

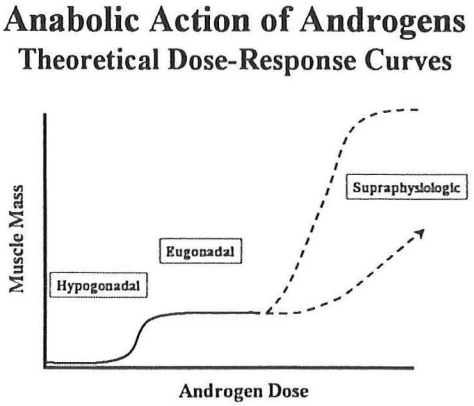
"Inside the Numbers"

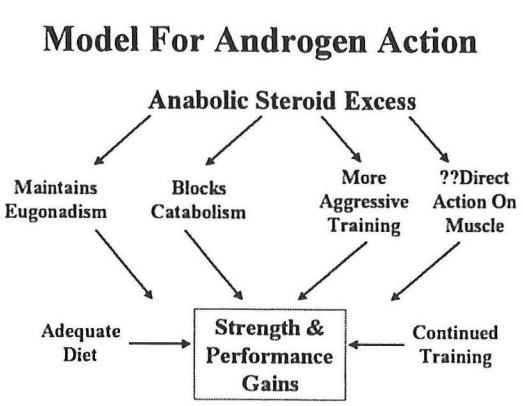
Bhasin et al

	No Exercise		+ Exercise	
	Placebo	Test.	Placebo	Test.
$\frac{\Delta Bench}{\Delta Wt}$	0	2.2	8.4	2.8
$\frac{\Delta Squat}{\Delta Wt}$	1.8	2.9	18	4.7

Although the landmark study of Bhasin's group demonstrated that supraphysiologic doses of androgens do work, their data cannot be extrapolated to these other populations for whom we really need anabolic agents. In this regard, Berger and colleagues have demonstrated less impressive beneficial effects of oxandrolone on improving weight gain and sense of well-being in HIV patients with involuntary weight loss(11). Oxandrolone (Oxandrin, not Anavar!) is now FDA approved (2.5-20 mg/day) for treatment of involuntary weight loss. With improved survival of patients with formerly terminal diseases (AIDS & other immunodeficiencies, cancer, trauma/burns, etc.), plus our aging population suffering from "sarcopenia" and frailty, you had better believe that anabolic agents will be in our armamentarium henceforth. Pharmaceutical companies are motivated to pursue anabolic agents because there is money to be made in this area, and it is the responsibility of academic medicine to understanding if drugs such as androgens can be used safely and effectively for this purpose.

Of course, Bhasin's study leaves us in another quandary, which is <u>why</u> do supraphysiologic doses of androgens promote weight and strength gains. The whole concept flies in the face of our understanding of hormone receptor mechanisms, because once a receptor is saturated, more agonist should have no further effect. Could there be a second androgen receptor, or is this some quasi-specific effect that never saturates?? We have a difficult time conceptualizing this process because we have only a very crude idea of the dose-response curve(12). Four points are worth mentioning in developing a model to explain the data. First, overtraining itself can lead to hypogonadism as seen in "anorexia athletica" of female distance runners and even wrestlers who cut weight and practice profusely. Androgen administration will blunt the ill effects of hypogonadism (first phase of the theoretical dose-response curve). Second, high intensity exercise activates cortisol production (stress response), and high concentrations of androgens can block cortisol binding to the glucocorticoid receptor(13), which could theoretically blunt the catabolic effects of cortisol. Third, the psychological effects of androgens promote more intense training, and finally, androgens may exert a direct action on muscle, which we will explore later. The key experiments to do are: 1) high dose androgen + AR antagonist and 2) high dose androgens in patients with complete androgen insensitivity.





IV. Side Effects

Are androgens bad for you?

Like many things in life, androgen self-administration is a risk/benefit proposition that is a matter of judgement. The problem with this topic is that some side effects are common, and others are rare. It is difficult to prove that the rare side effects are due to the androgens, and it is difficult to convince serious users that the side effects outweigh the benefits because it is a low percentage of users that will experience severe problems.

Cardiovascular: Hypertension is common amongst androgen abusers, and several reports of abusers dying with hypertrophic cardiomyopathy (cor bovinum), strokes, and myocardial infarctions have appeared. Autopsies have failed to show atherosclerosis but do show hypertrophic cardiomyopathy with fibrosis(14). Although it makes sense that cardiac hypertrophy (as occurs, incidentally, in acromegaly) from anabolic steroid excess might accompany skeletal muscle hypertrophy, the numbers are too small to prove cause and effect.

Liver: All oral androgens can cause cholestasis and hepatocellular damage, but this may not be due to their androgenic activity but rather a nonspecific effect of high doses of a xenobiotic. Some East German athletes receiving massive doses of turinabol required hospitalized for liver failure(9). Peliosis hepaticus, which is the development of venous lakes in the liver, and hepatocellular carcinoma were originally described in patients treated with oral androgens for aplastic anemia. It is fortunate for the NFL that these complications are uncommon even at the high dose used by professionals.

Lipids: All androgens lower HDL due to activation of hepatic lipase, but replacement doses of transdermal androgens lower HDL minimally. All oral androgens raise LDL, whereas physiological replacement doses of parenteral and transdermal testosterone do not raise and may in fact lower LDL in hypogonadal subjects.

Brain: My contention is that the sole compelling medical reason to restrict and to discourage recreational use of androgens is the profound psychological alterations frequently experienced by some predisposed androgen abusers. Feelings of euphoria and hypomania are common, but delusions and paranoia also occur(2). Increased libido is almost universal (although gender preference is not altered), and numerous cases of rapes and sexual abuse of children, murders, suicides, and homicides have been documented in androgen abusers(15). Increased aggression is common when sensitive testing measures are used, but frank "roid rage" is probably uncommon. A Scandinavian study documented an alarming increase in violent and premature deaths among weightlifters where androgen abuse is pervasive(16).

Pope's group repeated Bhasin's protocol of 600 mg/week of injectable testosterone to more carefully evaluate the psychological effects of androgen excess(17). They demonstrated dramatic increases in scores on the Young Mania Rating Scale and the Point Subtraction Aggression Paradigm (a computer provocation test of aggression). In fact, one subject had to be discontinued during the testosterone treatment period due to rapidly escalating manic symptoms. In truth, only 2/50 patients experienced marked increases in manic scores, but 6/50 experienced moderate increases, as opposed to one moderate response during the placebo administration. On the other hand, this dose is still well below what most androgen abusers use, and the duration of use was only 6 weeks, so it is likely a minimum estimate of potential for severe psychiatric symptoms developing during androgen abuse. Thus, although grave manic responses occur in some individuals, the response varies tremendously. While debilitating responses occur only in a minority of users, their data did not find characteristics that would allow one to predict which individuals are at risk for marked manic responses. The group reviewed comparable studies and concluded that about 5% of users experience serious psychiatric disturbance from androgens whereas about 10% experience demonstrable but subclinical disturbance; however, the majority of users are not significantly affected. Still, 5% of >1,000,000 users is 50,000 people, and we have plenty of crazy people in this country already.

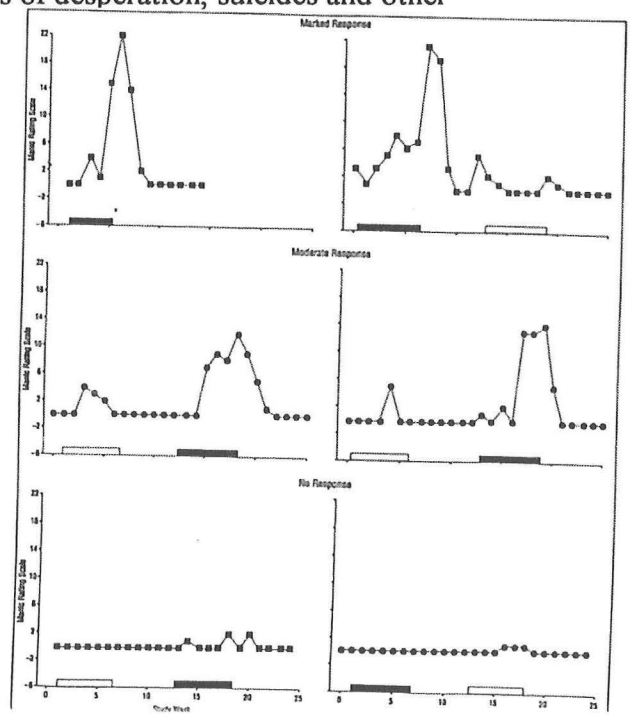
In the extreme, intense cycles of overtraining, dose escalation, rising manic symptoms, and enduring withdrawal periods can lead to physical and mental decompensation known as the "roided out" syndrome (like being an intern on call at Parkland for 5 days straight). During these periods of desperation, suicides and other forms of catastrophic demise can occur(18).

Supraphysiologic Testosterone
Effects On Mood & Aggression

	Placebo		Testosterone	
	Start	End	Start	End
YMRS	0.3	1.1	0.5	3.9**
PSAP	208	222	208	362*
Manic Score	7.9	7.4	7.5	9.2**
Liking Score	50	50	51	55**

*p<0.05
**p<0.01

Pope et al Arch Gen Psychiatry 57:133-140 (2000)



Males: Infertility and testicular atrophy are extremely common yet rarely concern abusers. Gynecomastia occurs commonly with aromatizable testosterone derivatives. Reports of urinary retention from premature prostatic hyperplasia have appeared, and based on our knowledge of prostate biology it is pretty safe to assume that the androgens played a role. A few cases of prostate cancer in young men have been reported as well.

Females: You really have to be serious to use androgens if you are a woman. Menstrual irregularity and breast atrophy occurs rapidly in the majority of serious users; libido soars(9,19). Parenthetically, several pharmaceutical companies are developing testosterone preparations to treat "female sexual dysfunction" a non-disease that was invented to allow the sale of a drug to make women more interested in having sex. With prolonged exposure, clitoromegaly, deepening of the voice, and hirsutism follow, and many of these changes are irreversible. Women who repeatedly take large doses of androgens can be easy to spot, although shrewd athletes that take brief cycles out of competition can be difficult to identify. Heidi Krieger, an East German shot put star was so virilized by 3+ grams of turinabol per year(9) that she eventually changed her gender.

Miscellaneous: Children will experience premature epiphyseal plate fusion and pubertal progression, particularly with aromatizable androgens. Infections acquired from pareneral androgens range from abcesses at injection sites to HIV and hepatitis from sharing needles. Acne can be very severe and occur on unusual places such as the back—pustular acne on the back is a pretty good indication of an androgen abuser. Pattern baldness, striae, edema, and polycythemia occur but are usually mild. Tendon rupture is a well-recognized problem by users, but ultrastructural studies have failed to demonstrate abnormalities in tendon composition(20). These ruptures may be simply a consequence of the aggressive overtraining by these athletes.

Finally, androgen abuse has been associated with abuse of other substances(21), and this association has become stronger over the years(18,22). Although the tendency to polysubstance abuse is not terribly surprising, it does complicate interpretation of anecdotal reports blaming ill effects on androgens alone. Lyle Alzado, before he died of a brain tumor, was convinced that his years of supraphysiologic androgen self-administration were responsible for his cancer, but it would not be surprising if he had acquired other ailments related to risk-taking behaviors.

Most users consider these ill-effects and risks to be well worth the benefits of size, strength, and performance. Although some of us would not accept a 5% risk of anything, the mindset of most recreational users (let alone elite athletes) is such that they are quite willing to accept these risks. You will not convince a dedicated user that the danger to his liver and heart or the impending sperm count reductions is sufficient reason to abandon androgen abuse.

V. Drug Testing Technology

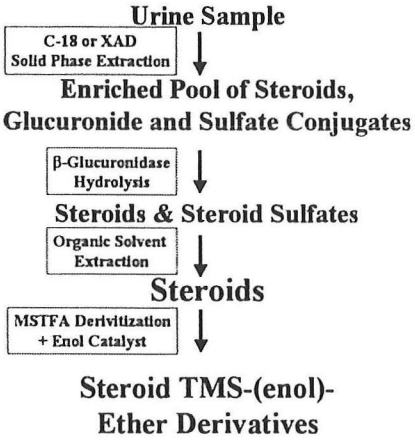
What does it mean to fail a drug test?

Conventional testing schemes involve hydrolysis, extraction, derivitization, and gas chromatography/mass spectrometry of urinary steroids and steroid conjugates(23). This is great for detecting unnatural steroids (nandrolone, stanozolol, oxandrolone), but serious professionals do not use these any more (except the dumb ones) because they will get caught. Injectable nandrolone esters are slowly hydrolyzed and leak metabolites into the circulation for weeks to months. Although a trace of nandrolone is found in normal people (probably of gonadal origin(24)) elevated quantities of metabolites, such as 19-norandrosterone and 19-noreticholanolone, are frequently the compounds detected in drug tests, especially because of the belief that nandrolone esters protect against tendon rupture.

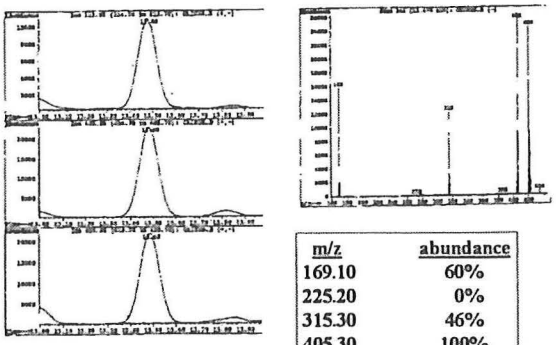
So how do you know if someone is instead taking the naturally-occurring androgens testosterone or dihydrotestosterone? This is a much more difficult problem that was first addressed by measuring the ratio of testosterone to epitestosterone (the 17α-epimer of testosterone, or Epi-T)(23). Ordinarily, T and Epi-T are produced in roughly equal amounts, so administration of exogenous T elevates the T/Epi-T ratio. Values > 6 are suggestive of exogenous T administration, but there is considerable ethic variation in the normal range, with Asians having particularly high T/Epi-T ratios. The East Germans got wise to this right away and began making pharmaceutical grade Epi-T supplements for their testosterone-primed athletes to artificially lower their ratios back to normal(9). Dihydrotestosterone has such a short half-life that testing requires quantitating the ratios of 5α-reduced metabolites relative to 5β- or to non-5α-reduced C_{19} steroids. Using the latter test, 18 Chinese swimmers tested positive for DHT use at the Asian Games in 1994, with 7 busted for second confirmatory positive test(25).

To get around false positives, the groups of Catlin(26) and Shackleton(27,28) have developed isotope ratio mass spectrometry techniques for the analysis of metabolites normally present in urine. These techniques rely on fact that synthetic steroids derive from plant sterols, primarily diosgenin and stigmasterol. The plant enzymes discriminate between ^{12}C and ^{13}C isotopes more than mammalian enzymes, such that the ^{13}C content (normally 1% natural abundance) is slightly higher for endogenous steroids than for those synthesized from plant sterols. This difference ($\delta^{13}C\%\%$) is a tiny number that can be measured very accurately and reproducibly by the incredibly precise isotope ratio mass spectrometer.

Unfortunately, I have to agree with Jean that athletes and their coaches will simply get around this methodology by having custom labs make steroids from animal-derived precursors or by subverting tests by other means. The advances in detection technology will simply raise the bar such that gaining the androgen advantage will be more costly and treacherous, but the serious competitors will find ways to get it done.



19-Noretiocholanolone



m/z	abundance
169.10	60%
225.20	0%
315.30	46%
405.30	100%
420.30	92%

DHT: Chinese Women Swimmers

Athlete	DHT_{corr}	5α/5β-A	5αA/Etio	DHT/EpiT
1	388.67	56.61	5.70	83.14
2	89.54	12.65	1.99	24.77
2	60.73	10.21	1.92	13.22
2	77.40	10.62	1.99	29.07
2	47.93	17.75	2.26	17.43
3	18.63	14.02	2.53	4.73
4	16.38	67.88	2.91	9.38
5	28.70	62.45	2.52	6.42
5	15.68	70.52	2.51	7.80
Upper Limit:	12.13	1.88	2.20	2.72

$\delta^{13}C$ Values For High T/EpiT Ratio

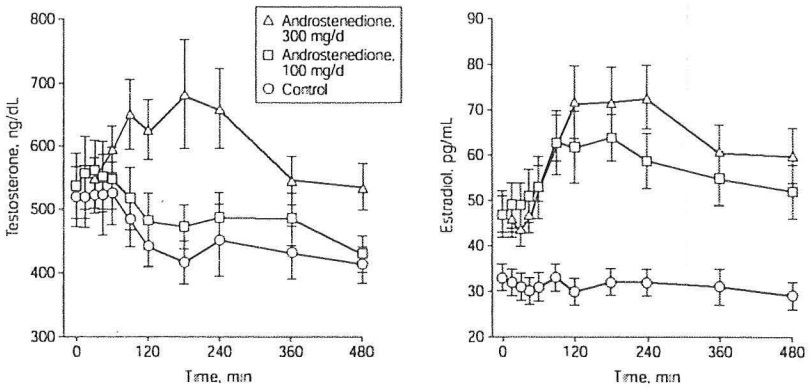
Athlete	T/Epi-T	5βA	5αA	5βP	5βP-5βA	5βP-5αA
1	40	-30.42	-31.96	-25.67	4.8	6.3
2	29	-31.43	-34.57	-26.14	5.3	8.4
3	80	-28.76	-31.25	-23.06	5.7	8.2
4	10	-25.32	-25.76	-24.54	0.8	1.2
5	9	-24.82	-25.47	-23.49	1.3	2.0
6	8	-24.62	-26.04	-23.36	1.3	2.7
Control		-25.69	-26.35	-24.26	1.43	2.09
SD		0.92	0.68	0.70	0.68	0.63

VI. Precursor Steroids and the Neutraceutical Industry

Is androstenedione really a food supplement??

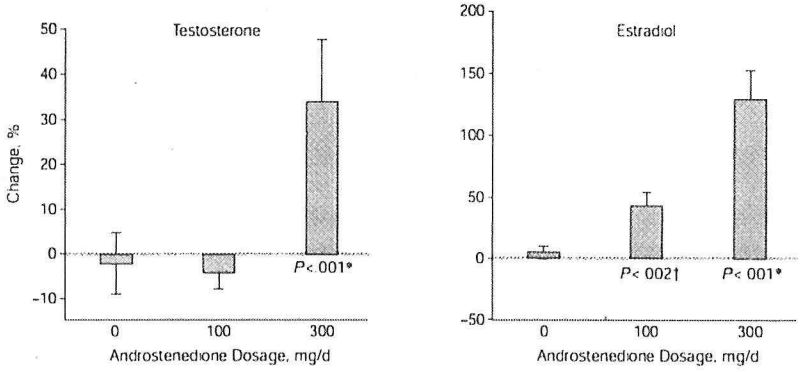
Of course not, but yet millions of dollars are spent on it and other "inactive" steroids daily thanks to the Dietary Supplements Health and Education Act of 1994 (DSHEA). You simply need to claim that something (pure compound, extract, herb, whatever) is a "dietary supplement" and has some benefit for "structure or function" to put it on the market. You do not need to prove efficacy or safety. This incomprehensibly irresponsible piece of legislation has done more to erase 50 years of progress in pharmaceutical safety than any other action by either government or industry. Once Mark McGwire let out that he was using "andro" during his 70 home-run year, much interest developed in studying androstenedione, which is one step away from testosterone. Alas, 300 mg of androstenedione only mildly raise serum testosterone concentrations transiently(29,30), but estrogens go way up, and strength improvements have not been demonstrated(31,32). Failure to raise testosterone significantly is likely due to the abundance of 17βHSDII in peripheral tissues, whereas 17βHSDIII is restricted to the testes and 17βHSDV is an inefficient and labile enzyme. Furthermore, oral androstenedione consumption leads to 19-norandrosterone and 19-noretiocholanolone in the urine(33), probably by metabolism of either androstenedione itself or a contaminant. This, of course, will be interpreted as a positive test for nandrolone.

Figure 1. Mean Serum Testosterone and Estradiol Concentrations, Day 7



To convert values for testosterone to nmol/L, multiply by 0.0347, to convert values for estradiol to pmol/L, multiply by 3.76. Error bars represent SE.

Figure 2. Mean Percentage Change in Area Under the Curve for Serum Testosterone and Estradiol Concentrations, Days 1 and 7



Values are presented as the averages for days 1 and 7. Asterisk indicates *P* value for comparison vs control and 100-mg/d groups. Dagger indicates *P* value for comparison vs control group. Error bars represent SE.

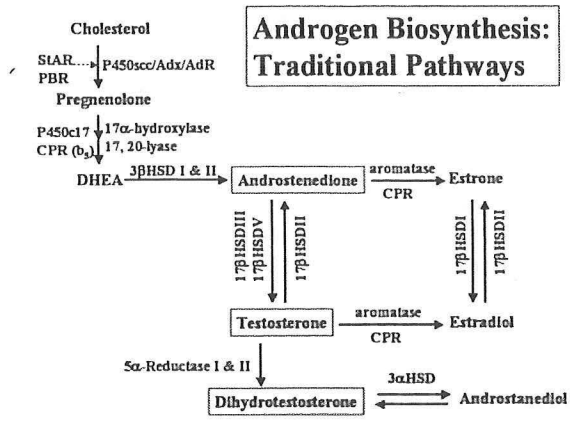


Table 1. Summary of the Purity and Content of Capsules of Over-the-Counter Androstenediones*

Brand No.	No. of Capsules Tested	Steroid and Dose Listed on Label†	Steroids Found	Mean Amount, mg
1‡	13	Androstenedione, 100 mg	Androstenedione	93.1§
2	5	Androstenedione, 100 mg	Androstenedione	82.8‖
3	4	Androstenedione, 100 mg	Androstenedione	103
4	2	Androstenedione, 100 mg	Androstenedione	90
5	4	Androstenedione, 100 mg	Androstenedione	68
6	4	Androstenedione, 100 mg	Androstenedione	65
7	4	4-Androstene 3, 17-dione, 50 mg¶	4-Androstene 3, 17-dione	35
8	4	Androstenedione, 50 mg	None	0
9	4	4-Androstene 3, 17-dione, 250 mg¶	4-Androstene 3, 17-dione	168
		(not listed on label)	Testosterone	10

*Brands 1 and 2 and 3 through 9 tested for impurities at 0.1% and 1%, respectively.
†Exactly as listed on the label.
‡Brand used for our study in reference 9.
§Range, 84-107 mg.
‖Range, 76-84 mg.
¶4-Androstene 3, 17-dione = androstenedione.

Table 2. Number of Subjects Categorized by Concentration and Mean Concentration of 19-Norandrosterone in Urine Samples Collected 0 to 8 Hours After Administration of 100 or 300 mg of Androstenedione*

	No. of Subjects					
Dose, mg	<0.5 ng/mL	0.5-2.0 ng/mL	2.1-5.0 ng/mL	5.1-10 ng/mL	11-35 ng/mL	Mean (SD) Concentration, ng/mL
0	13	0	0	0	0	0
100	0	3	7	3	0	3.8 (2.5)†
300	0	1	1	5	4	10.2 (8.9)

*Sports test results were considered negative when concentrations were less than or equal to the 2.0 ng/mL cutoff and positive when concentrations were greater than 2.0 ng/mL.
†Significantly different from the 300-mg dose ($P = .006$).

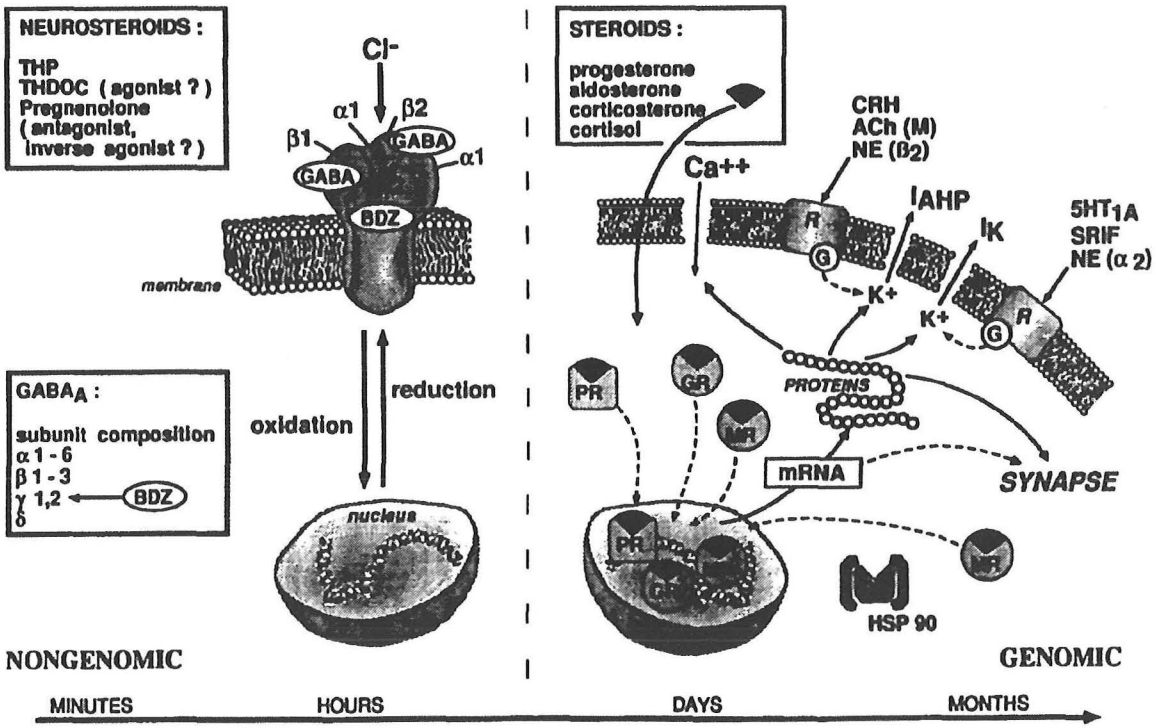
DHEA, only 2 steps from testosterone, is another hot topic (for another day), and although it can be converted to androgens, the conventional 50 mg/d dose does not change testosterone concentrations in men while it doubles testosterone values in postmenopausal women(34). DHEA has been shown to have action on neurons and ion channels, suggesting that it may be a useful treatment for aging and senility. In a broader sense, a whole class of compounds collectively known as "neurosteroids" derives from pregnenolone and progesterone(35). These compounds, primarily 3α and/or 5α reduced steroids, are not traditional hormones with cognate nuclear receptors, but they bind to ion channels such as the GABA receptor chloride channel complex and potentiate GABA action (and thus are anxiolytic)(36-38). I keep waiting for allopregnanolone to hit the market, but I have not seen it yet. In fact, an allopregnanolone analog called alphaxolone was developed for use as an anaesthetic agent years ago.

The actions of neurosteroids on ion channels leads to an apparent dichotomy of more traditional steroids (testosterone, dihydrotestosterone) that bind to nuclear receptors and act over hours to modulate gene expression versus non-traditional steroids (allopregnanolone, pregnenolone sulfate) that act rapidly on ion channels to send signals over seconds to minutes. However, recent studies show that androgens, including synthetic androgens, can modulate ion currents(39), and our lab has recently shown that

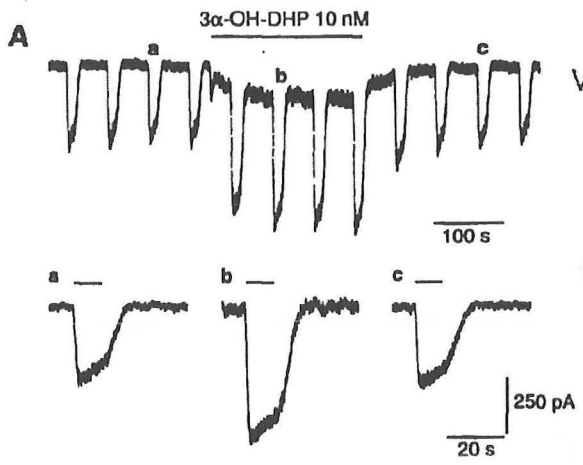
neurosteroids can be metabolized to C_{19} androgen precursors by human P450c17. Thus this distinction is blurred, and it is impossible to predict what will happen when one takes hundreds of milligrams of any steroid, especially when there is no assurance of purity!!

I propose that at least part of the anabolic actions of androgens are mediated direct action on ion channels within neuromuscular units. This hypothesis may explain the need for supraphysiologic doses and differences in responses of one individual to different androgens. Genetic differences in ion channel subunits and neurotransmitter pathways may also explain the variable efficacy and susceptibility to side effects, particularly psychiatric manifestations, among users.

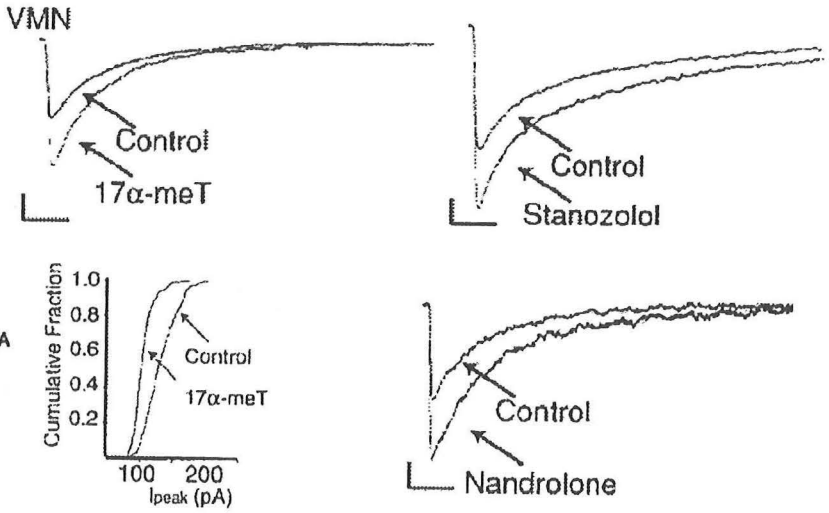
Regardless, it is clear to me that the endocrine community can no longer passively dismiss the use of androgens for anabolism as silly, misguided attempts by a few renegades to score points in sports or in the dating game. Control over androgen precursors has slipped by us, and their marketing is now legal and totally out of control. Rather, the anabolic action of androgens is a difficult but fascinating scientific topic that covers many fields from enzymology to neurobiology, transcriptional regulation, and genetics. This field represents both an opportunity for tremendous benefit in the elderly and in debilitated populations and a potential for widespread damage in at-risk populations. This is not an area that we want to sit back and let entrepreneurs and infomercials tell our patients what is good for them. Rather, investigators must explore this field with the same rigorous, objective scientific approach that is applied to any other problem, to determine the true risks, benefits, and appropriate use and safeguards of androgens and other anabolic agents. Perhaps most troubling, this field will require that we draw the line between medical benefit and cosmetic enhancement. We all want to be youthful, fit and buff, but where does prevention of frailty and its consequences end and vanity begin? I hate to end on philosophical notes, but this is yet another twist in this terribly twisted topic.



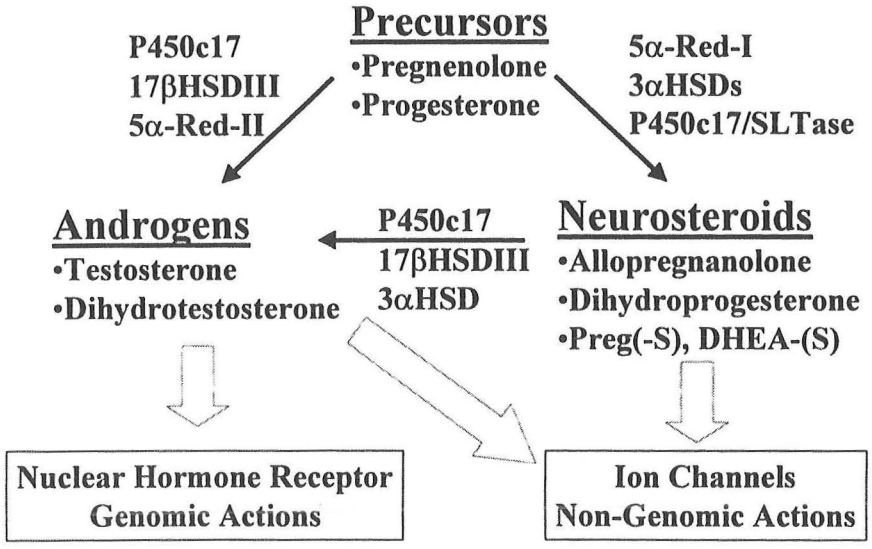
Allopregnanolone: Potentiation of GABA Action



Synthetic Androgens Potentiation of GABA/Cl⁻ Currents



Neurosteroids & Androgens



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